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(57) Abstract

This invention relates to 3,4-dinitrobenzamide compounds which are ligands, in particular, antagonists, of the Calcitonin Gene-Related Peptide ("CGRP") receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CGRP, including, but not limited to, headaches, especially migraines; non-insulin dependent diabetes mellitus; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, by the use of 3,4-dinitrobenzamide CGRP receptor antagonists.

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COMPOUNDS AND METHODS

FIELD OF THE INVENTION

This invention relates to 3,4-dinitrobenzamide compounds which are ligands, in particular, antagonists, of the Calcitonin Gene-Related Peptide (hereinafter "CGRP") receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CGRP, including, but not limited to, headaches, especially migraines; non-insulin dependent diabetes mellitus ("NIDDM"); neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, preferably humans, by the use of CGRP receptor ligands, in particular, 3,4-dinitrobenzamide antagonists, thereof.

BACKGROUND OF THE INVENTION

CGRP is a 37 amino acid polypeptide that is stored and released from nerve terminals in both the central nervous system and the peripheral nervous system. (Goodman et al., *Life Sci.*, Vol. 38, pp. 2169-2172 (1986)). CGRP has been detected in nerves innervating the heart, peripheral and cerebral blood vessels, and kidneys by immunohistochemical and radioimmunoassay methods. (Yamamoto et al., *Prog. Neurobiol.*, Vol. 33, pp. 335-386 (1989)). CGRP has been shown to mediate its biological response by binding to specific cell surface receptors that have been identified in a variety of tissues. Evidence from biochemical studies suggest that CGRP receptors belong to the family of G-protein coupled receptors. The widespread distribution of CGRP receptors on muscle, glandular, epithelial and neuronal cells is consistent with its wide range of biological actions, including pain transmission (Collin et al., *Pain*, Vol. 54, p. 20 (1993); and *J. Neurosci.*, Vol. 16, No. 7, pp.2342-2351 (1996)); peripheral and cerebral vasodilation (Brain et al., *Nature*, Vol. 313, pp. 54-56 (1985)); cardiac acceleration (Sigrist et al., *Endocrinology*, Vol. 119, pp. 381-389 (1986)); regulation of calcium metabolism (Grunditz et al., *Endocrinology*, Vol. 119, pp. 2313-2324 (1986)); reduction of intestinal motility (Fargeas et al., *Peptides*, Vol. 6, pp. 1167-1171 (1985)); regulation of glucose metabolism, e.g., reduction of insulin secretion and insulin sensitivity, (Hermansen et al., *Peptides*, Vol. 27, pp. 149-157 (1990); and Molina et al., *Diabetes*, Vol. 39, pp. 260-265 (1990)); reduction of appetite and reduction of growth hormone increase (Tannenbaum et al., *Endocrinology*, Vol. 116, pp. 2685-2687 (1985)); reduction of inflammation of the skin, for example in allergic contact dermatitis (Gutwald et al., *J. Invest. Derm.*, Vol. 96, pp. 695-698 (1991)) and other inflammatory skin conditions (Buckley et al., *Neuroscience*, Vol. 48, pp.

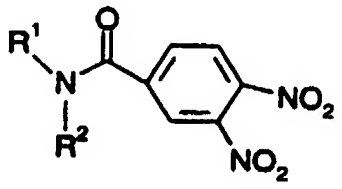
963-968 (1992); and Escott et al., *Br. J. Pharmacol.*, Vol. 110, pp. 772-776 (1993)).

Since CGRP has a number of effects on the cardiovascular, central nervous, gastrointestinal, respiratory, and endocrine systems, it has now been discovered that limited and selective inhibition of CGRP receptor mechanisms represents a novel preventative and therapeutic approach to the treatment of a broad variety of disease states that are mediated by CGRP. In particular, the development of an active CGRP receptor antagonist would be expected to be useful in the treatment of a variety of disease states that are mediated by CGRP including, but not limited to, headaches, especially migraines; NIDDM; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, preferably humans ("CGRP-mediated diseases").

Surprisingly, it has now been discovered that a class of non-peptide compounds, in particular 3,4-dinitrobenzamides of formula (I) function as CGRP receptor antagonists, and therefore, have utility in the treatment of disease states wherein inhibition of CGRP receptor mechanisms is indicated for prevention or therapeutic treatment thereof.

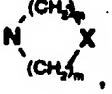
SUMMARY OF THE INVENTION

In one aspect, the present invention is to a genus of novel compounds of formula (I), or pharmaceutically active salts thereof, said compounds which are also useful in treating the above-mentioned CGRP-mediated disease states:

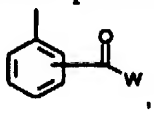


Formula (I)

wherein:

R^1 is hydrogen, methyl, $-(CH_2)_n$, branched (3-6 carbon) alkyl, $-(CH_2)_n$phenyl, $-(CH_2)_n-N$  , wherein X is CH_2, oxygen or N-alkyl, or R^1 is $-(CH_2)_nNR^3R^4$, or $-(CH_2)_nZ$, wherein Z is $-CO_2H$, $-CO_2$-alkyl, $-CONR^3R^4$, $-N(R^3)CO_2R^3$, $-N(R^3)C(O)NR^3R^4$, $-OC(O)NR^3R^4$, or $-COR^5$, and wherein R^3 and R^4 are independently hydrogen, $-C_{1-4}$alkyl or $-C_{1-4}$alkylphenyl, or together with the

nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring, wherein the heteroring is optionally fused to an optionally substituted phenyl ring, and R^5 is methyl, trifluoromethyl, C_{2-6}alkyl, phenyl or heteroaryl;

R^2 is optionally substituted aryl or heteroaryl, or R^2 is A-Ar, wherein A is lower alkyl (C_{1-4}) or branched alkyl, wherein a branch may contain a substituted phenyl ring, and Ar is substituted phenyl or a substituted 5- or 6-membered heteroaryl ring which optionally contains one or more heteroatoms selected from N, O or S, or R^2 is  , wherein W is -OH, $-NR^3R^4$, -O-alkyl, an amide derived from an amino acid, NR^6R^7, where R^6 is H, alkyl, and R^7 is aryl or substituted aryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-substituted aryl, $-(CH_2)_n$-heteroaryl, or $-(CH_2)_n$-Z; or

R^1 and R^2 together with the nitrogen to which they are attached form a 5- or 6-membered heteroring fused to an optionally substituted phenyl ring;

m is 1 to 3; and

n is 1 to 6, provided that the compound is not N-3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1-H-3-benzazepine-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3,4-dinitrobenzamide or N-phenyl-3,4-dinitrobenzamide.

In another aspect, the present invention is to a method of treating CGRP mediated diseases, all in mammals, preferably humans, comprising administering to such mammal in need thereof, an effective amount of a 3,4-dinitrobenzamide compound of formula (I), or a pharmaceutically active salt thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically active salt thereof, and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating CGRP-mediated disease states, including, but not limited to headaches, especially migraines; NIDDM; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, all in mammals, preferably humans.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that 3,4-dinitrobenzamide compounds of formula (I) are CGRP receptor ligands, in particular, antagonists thereof. It has also now been discovered that selective inhibition of CGRP receptor mechanisms by treatment with the receptor ligands of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of CGRP-mediated disease states.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heteroring" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 5-, 6-, or 7-membered ring system which contains one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, thiazole, immidazole, thiadiazole or triazole.

The terms "aryl" or "heteroaryl" are used herein at all occurrences to mean substituted and unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems and heteroaryl moieties, which may include, but are not limited to, heteroatoms selected from O, N, or S. Representative examples include, but are not limited to, phenyl, benzyl, naphthyl, pyridyl, quinolinyl, thiazinyl, and furanyl.

The term "optionally substituted" is used herein at all occurrences to mean that the moieties may or may not be substituted with one to three various functional groups including methoxy, hydroxy, phenoxy, trifluoromethyl, C_{1-4}alkyl, halo, nitro, CN, C(O)OH, C(O)NR'R", wherein R' and R" are independently hydrogen or C_{1-4}alkyl. It will be understood that the optional substituent(s) may be at a position ortho, meta or para relative to the nitrogen of the amide functionality of formula (I). Preferably, the optional substituent(s) are positioned ortho relative to the nitrogen of the amide functionality of formula (I).

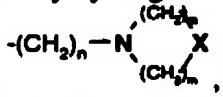
The term "CGRP mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by Calcitonin Gene-Related Peptide.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloric, sulfate, phosphate, diphosphate, hydrobromide and nitrate or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate and stearate. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

For the compounds of formula (I) various embodiments are as follows.

R^1 is suitably hydrogen, methyl, -$(CH_2)_n$, branched (3-6 carbon) alkyl, -$(CH_2)_n$phenyl,  , wherein X is CH_2, oxygen or N-alkyl, or R^1 is -$(CH_2)_nNR^3R^4$, or-$(CH_2)_nZ$, wherein Z is -CO_2H, -CO_2-alkyl, -$CONR^3R^4$, -$N(R^3)CO_2R^3$, -$N(R^3)C(O)NR^3R^4$, -$OC(O)NR^3R^4$, or -COR^5 wherein R^3 and R^4 are independently hydrogen, C_{1-4}alkyl or C_{1-4}alkylphenyl, or together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring, wherein the heteroring is optionally fused to an optionally substituted phenyl ring and R^5 is methyl, trifluoromethyl, C_{2-6} alkyl, phenyl or heteroaryl. R^1 is preferably -$(CH_2)_nZ$, wherein Z is -CO_2H, -CO_2-alkyl, wherein alkyl is tert-butoxy, or -$CONR^3R^4$, wherein R^3 and R^4 are independently hydrogen, or C_{1-4}alkylphenyl, C_{1-4}alkyl, -$(CH_2)_nNR^3R^4$, wherein n is 2 or 3, and R^3 and R^4 are both C_{1-3}alkyl or R^3 and R^4 form a 5-, 6- or 7-membered heteroring, preferably morpholino, piperidinyl, or piperazine, or wherein the heteroring is optionally fused to an optionally substituted phenyl ring, such as a benzazepine.

R^2 is suitably optionally substituted aryl or heteroaryl, or R^2 is A-Ar, wherein A is lower alkyl (C_{1-4}) or branched alkyl, wherein a branch may contain a substituted phenyl ring, and Ar is substitued phenyl or a substituted 5- or 6-membered heteroaryl ring which optionally contains one or more heteroatoms selected from N, O or S. R^2 is preferably aryl, more preferably phenyl. Suitable substituents for Ar are C_{1-4}alkyl, halo, cyano, trifluoromethyl, trifluoromethoxy, alkoxy, nitro, and aryl. Preferably, Ar is substituted by C_{1-4}alkyl, most preferably ethyl.

R^1 and R^2 together with the nitrogen to which they are attached suitably form a 5- or 6-membered heteroring fused to an optionally substituted phenyl ring.

Among the preferred compounds of the invention are the following compounds:

N-(2-ethylphenyl)-N-[2-(tert-butoxycarbonyl)ethyl]-3, 4-dinitrobenzamide;
N-[2-(morpholinocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-(ethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-(diethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-[(1-piperidinyl)carbonyl]ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-(3-oxo-3-phenylpropyl)-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-Methyl-N-(2-methylphenyl)-3, 4-dinitrobenzamide;
N-(2-ethylphenyl)-N-methyl-3, 4-dinitrobenzamide;
N-(2, 6-diethyl)phenyl-N-methyl-3, 4-dinitrobenzamide;
N-[3-(2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(7, 8-dimethoxy-2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(N'-methyl-2-phenylethylamino)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(morpholin-4-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide;
N-[3-(piperidin-1-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide;
N-[2-(N', N'-dimethylamino)ethyl]-N-phenyl-3, 4-dinitrobenzamide;
N-(3-methylbutyl)-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide; and
N-methyl-N-phenyl-3, 4-dinitrobenzamide.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an

amount sufficient to treat headaches, especially migraines; NIDDM; neurogenic inflammation; cardiovascular disorders; chronic inflammation; pain; endotoxic shock; arthritis; allergic rhinitis; allergic contact dermatitis; inflammatory skin conditions; and asthma, with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CGRP mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much

as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as

propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating CGRP-mediated diseases with an antagonist as depicted in formula (I). By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for a CGRP-mediated disease state, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

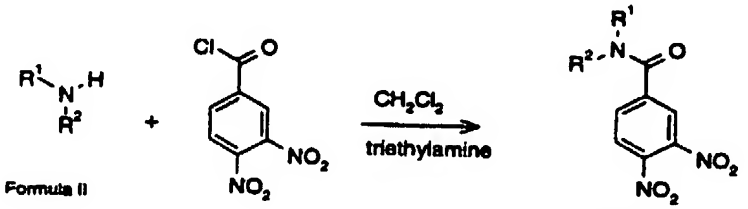
The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of

the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods of Preparation

Generally, the compounds of the invention may be prepared by the following reaction sequence:



Formula II Formula I

The reaction sequence involves the reaction of a compound of Formula II, wherein R^1 and R^2 are defined above, and a suitable acid chloride derived from 3, 4-dinitrobenzoic acid. This reaction may be accomplished in any of a variety of reaction inert solvents by mixing approximately equimolar amounts of a compound of Formula II and the acid chloride in the presence of an amine base at or below room temperature. The proper choice of reaction variables is within the skill of the art. Methylene chloride is the preferred solvent. Suitable amine bases are triethylamine, N-methylmorpholine, pyridine, and the like. In general, the reaction is allowed to proceed for about 1 hour to about 24 hours at which time the reaction is substantially complete. The completeness of a particular reaction may be measured by known techniques such as thin layer chromatography. The products of the reaction are isolated and purified by standard procedures. For example, the reaction mixture may be concentrated by evaporating the solvent and the residue may be partitioned between water and a convenient nonwater-miscible organic solvent such as ether, ethyl acetate, and the like. The solvent may then be evaporated and the residue chromatographed, for example, on silica gel. Choice of the proper chromatography solvent is within the skill of the art. After, or instead of, chromatography, the product may be recrystallized.

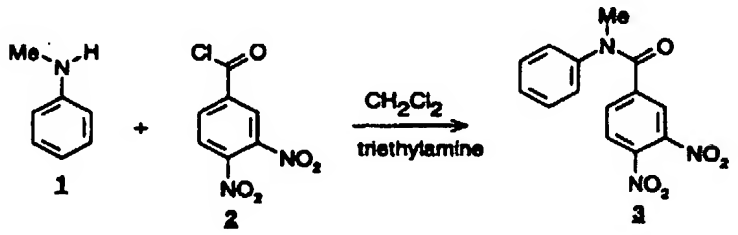
Acid addition salts may be prepared using standard procedures. For example, a hydrochloride salt may be prepared by dissolving the free base in a convenient solvent and treating this solution with a solution of hydrogen chloride dissolved in the solvent of choice. The acid addition salts may be reconverted to

the respective free base by treatment with a dilute solution of sodium hydroxide or potassium carbonate, for example.

The compounds of formula (I) are prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Specifically, compounds of formula I can be prepared according to Scheme 1 (Example 8). Formation of the desired amide (**3-Scheme 1**) is achieved by the reaction of an amine, such as N-methylaniline (**1-Scheme 1**), with an acid chloride derived from 3, 4-dinitrobenzoic acid (**2-Scheme 1**). This is performed in an inert solvent such as methylene chloride in the presence of an amine base such as triethylamine at or below room temperature. If the amine (**1-Scheme 1**) contains a basic amino group elsewhere in the molecule, such as in Example 6, the triethylamine may be omitted.

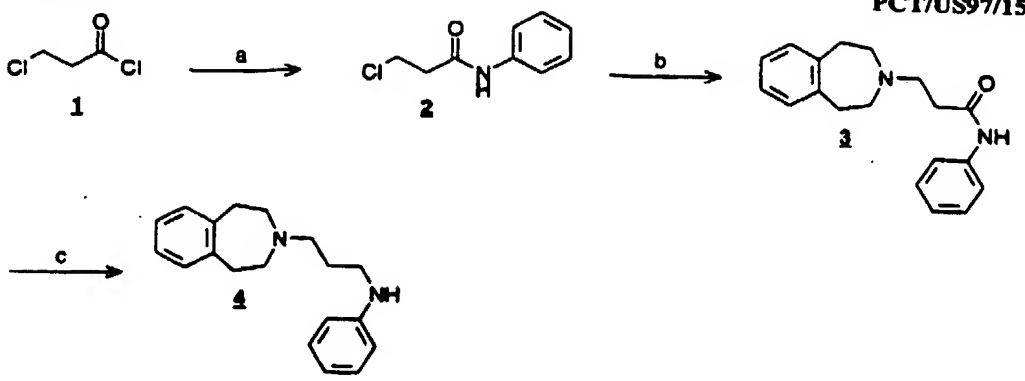
Scheme 1



In the event that the desired amine (**1-Scheme 1**) is not commercially available it may be prepared according to Schemes 2 or 3. The present invention includes such novel amine intermediates useful in the preparation of a variety of the final compounds of this invention.

Scheme 2 illustrates the case where the amine (**1-Scheme 1**) contains a second amine containing group such as in Example 1.

Scheme 2

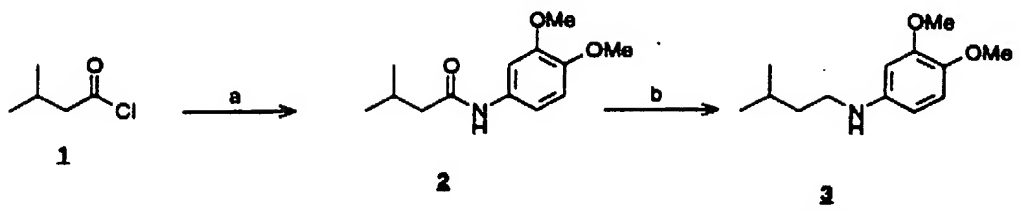


Reagents: a) aniline, CH_2Cl_2, pyridine; b) 2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride, triethylamine, acetonitrile, cat. nBu_4NI; c) $LiAlH_4$, THF, reflux.

In this example, 3-chloropropionyl chloride (**1-Scheme 2**) is reacted with aniline in an inert solvent in the presence of an amine base such as pyridine. This provides the 3-chloroamide (**2-Scheme 2**) which is then reacted with the 3-benzazepine compound in acetonitrile to provide amide (**3-Scheme 2**). This amide (**3-Scheme 2**) is next converted to the desired diamine (**4-Scheme 2**) via reduction using a reagent such as lithium aluminum hydride at reflux in tetrahydrofuran. The synthesis is then completed using (**4-Scheme 2**) according to Scheme 1.

In the case where the desired amine is not commercially available and does not contain an additional amino group, as in Example 7, the amine may be prepared according to Scheme 3. In this example isovaleryl chloride (**1-Scheme 3**) is reacted with 3, 4-dimethoxyaniline in the presence of an amine base such as triethylamine in an inert solvent such as methylene choride. This provides amide (**2-Scheme 3**) which is then converted into the required amine (**3-Scheme 3**) by reducing the amide functionality by methods previously described. The synthesis is then completed using (**3-Scheme 3**) according to Scheme 1.

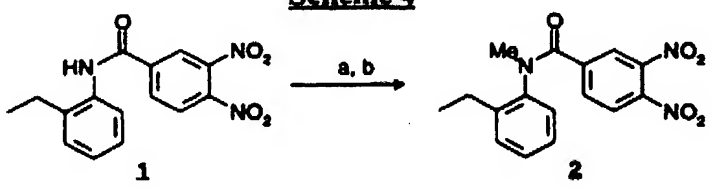
Scheme 3



Reagents: a) 3, 4-dimethoxyaniline, CH_2Cl_2, triethylamine; b) $LiAlH_4$, THF, reflux.

For the cases where the desired N-methyl anilines are not commercially available, they are readily prepared from the anilines via a number of methods well known in the art. One such method is that reported by Barluenga et al. (*J. Chem. Soc. Chem. Commun.*, pp. 1334-1335 (1984)). Alternatively, the desired N-methyl amides are obtained directly from the secondary amides via alkylation of the amide anion as illustrated in Scheme 4.

Scheme 4

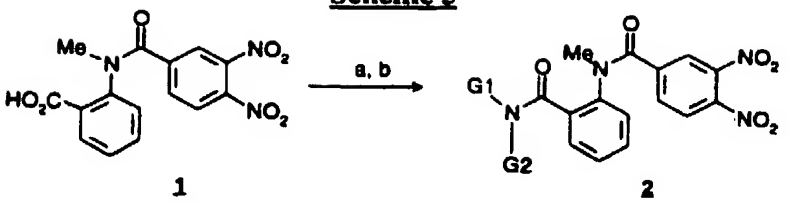


Reagents: a) $KN(SiMe_3)_2$, THF; b) Methyl iodide.

In this example, the secondary amide (**1-Scheme 4**) is treated with a non-nucleophilic base such as potassium bis(trimethylsilyl)amide [$KN(SiMe_3)_2$] at or below room temperature in a solvent such as tetrahydrofuran. The reaction solution is then treated with a suitable methylating agent such as methyl iodide. The resulting N-methyl amides (**2-Scheme 4**) are then recovered using standard isolation and purification methods.

Preparation of the compounds in which the ortho position of the phenyl ring contains an amide functionality (e.g., **2-Scheme 5**) begins with the ortho carboxylic acid **1-Scheme 5** (Example 32). Conversion of this acid to the acid chloride using a chlorinating agent such as thionyl chloride or oxalyl chloride followed by treatment with the desired primary or secondary amine (G1G2NH) produces the corresponding secondary or tertiary amide analogs (**2-Scheme 5**).

Scheme 5

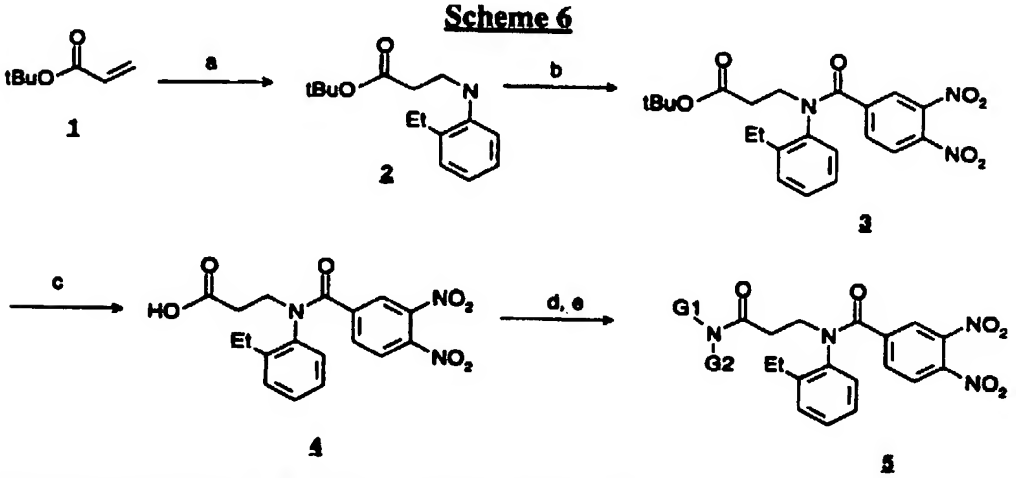


1 2

Reagents: a) thionyl chloride, $CHCl_3$; b) G1G2NH, triethylamine, CH_2Cl_2.

Compounds containing the N-propionate side chain (e.g., Examples 103-106, 108, 110, 111, 116) were prepared as outlined in Scheme 6. Michael addition of 2-ethylaniline to tert-butyl acrylate **1-Scheme 6** provides the alkylated aniline **2-Scheme 6**. This intermediate is next acylated with 3, 4-dinitrobenzoyl chloride as previously described to provide benzamide **3-Scheme 6** (Example 103). The tert-butyl ester is removed using an anhydrous acid such as trifluoroacetic acid (TFA) to give the carboxylic acid **4-Scheme 6** (Example 104). Conversion of this acid to the acid chloride using a chlorinating agent such as thionyl chloride or oxalyl chloride followed by treatment with the desired primary or secondary amine (G1G2NH) produces the corresponding secondary or tertiary amide analogs (**5-Scheme 6**). Alternatively, the acid chloride can also be treated with an alcohol in place of the amine to produce esters.

Scheme 6

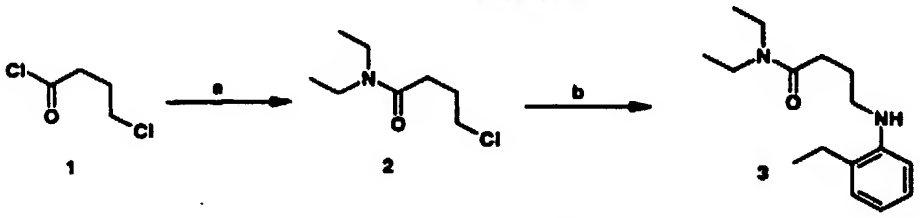


1 2 3 4 5

Reagents: a) 2-Ethylaniline, acetic acid, reflux; b) 3, 4-dinitrobenzoyl chloride, triethylamine, CH_2Cl_2; c) trifluoroacetic acid, CH_2Cl_2; d) oxalyl chloride, CH_2Cl_2; e) G1G2NH, triethylamine, CH_2Cl_2.

An alternative method for the preparation of compounds where R^1 is $(CH_2)_nZ$, is by alkylation of the desired aniline with an appropriate alkyl halide such as is illustrated in Scheme 7 for the preparation of Example 117. This procedure is quite general and may be used to prepare a wide range of anilines of which compound **3-Scheme 7** is just one example. In this particular example, 4-chlorobutyryl chloride (**1-Scheme 7**) is reacted with diethylamine to provide the diethylamide **2-Scheme 7**. Alkylation of 2-ethylaniline using **2-Scheme 7** as the alkylating agent then provides **3-Scheme 7**. Aniline **3-Scheme 7** is then acylated using 3, 4-dinitrobenzoyl chloride as previously described. In the compound of Example 118, the commercially available 3-chloropropiophenone is used in place of the amide **2-Scheme 7** in Scheme 7.

Scheme 7



Reagents: a) diethylamine, triethylamine, CH_2Cl_2, 0 °C; b) 2-ethylaniline, triethylamine, DMF, 100 °C.

EXAMPLES

Example 1. Preparation of N-[3-(2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide, hydrochloride

a) 3-Chloro-N-phenylpropanamide

Aniline (1.86 g, 20 mmol) in dry methylene chloride (50 mL) was treated with anhydrous pyridine (1.58g, 20 mmol), cooled to 0 °C, and treated with 3-chloropropionyl chloride (2.54 g, 20 mmol) in dry methylene chloride (5 mL). The mixture was stirred for 18h, allowing the ice bath to rise to room temperature. The reaction solution was washed with 10% HCl, water, and saturated sodium bicarbonate and dried (Na_2SO_4). Evaporation gave the title compound as a chalky white solid (3.8 g, 100%.). MS(ES) m/e 184 $[M+H]^+$.

b) 3-(2, 3, 4, 5-Tetrahydro-1H-3-benzazepin-3-yl)-N-phenylpropanamide

2, 3, 4, 5-Tetrahydro-1H-3-benzazepine hydrochloride (100 mg, 0.54 mmol) and 3-chloro-N-phenylpropanamide (110 mg, 0.60 mmol) were suspended in dry acetonitrile (2.5 mL) and treated with triethylamine (0.23 mL, 1.63 mmol)

and tetra-n-butylammonium iodide (20 mg, 0.05 mmol). The reaction was refluxed for 12h. The solvent was removed *in vacuo* and the residue was dissolved in methylene chloride and washed with water, 5% Na_2CO_3, and brine and dried (Na_2SO_4). The product was purified by flash column chromatography (silica, 50, 75, 90% ethyl acetate in hexane) to give 75 mg (50%) of a colorless amorphous solid. MS (ES) m/e 295.4 $[M+H]^+$.

c) 3-(2, 3, 4, 5-Tetrahydro-1H-3-benzazepin-3-yl)-N-phenylpropanamine

Amide from Example 1b (70 mg, 0.24 mmol) was dissolved in dry tetrahydrofuran (2.5 mL) and treated with lithium aluminum hydride (14 mg, 0.36 mmol). The reaction was refluxed for 3h. The reaction mixture was cooled to 0 °C and quenched with water (0.5 mL), 10% NaOH (0.5 mL), and water (0.5 mL). The solution was then stirred vigorously at room temperature for 15 min. The solution was diluted with ethyl acetate and dried over Na_2SO_4, filtered, and evaporated to give a dark colored oil. This material was dried under vacuum for 18h and then used directly for the following step. MS (ES) m/e 281.4 $[M+H]^+$.

d) N-[3-(2, 3, 4, 5-Tetrahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide hydrochloride

Diamine from Example 1c was dissolved in methylene chloride (1.5 mL), cooled in an ice water bath, and treated with 3, 4-dinitrobenzoyl chloride (41 mg, 0.18 mmol). After 30 min the cooling bath was removed and a thick solid began to form. An additional 1.5 mL of methylene chloride was added and the reaction was stirred at room temperature for an additional 2h. Dry diethylether was added and the solid was collected by filtration. Obtained 82 mg (67%, for two steps) of the title compound as an off-white powder. MS (ES) m/e 475.4 $[M+H]^+$, free base.

Example 2: Preparation of N-[3-(7, 8-dimethoxy-2, 3, 4, 5-tetrahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide hydrochloride

This compound was prepared according to the procedure described for Example 1 substituting 7, 8-dimethoxy-2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride for 2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride. Ruby glass. MS (ES) m/e 535.4 $[M+H]^+$.

Example 3: Preparation of N-[3-(N'-methyl-2-phenylethylamino)propyl]-N-phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 1 substituting N-methylphenethylamine for 2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride. The title compound was purified by flash column

chromatography (silica, 1, 2, 3% methanol in methylene chloride) to give a dark amber oil. MS (ES) m/e 463.4 $[M+H]^+$.

Example 4: Preparation of N-[3-(morpholin-4-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 1 substituting morpholine for 2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride and 3-chloro-N-(3, 4-dimethoxyphenyl)propanamide for 3-chloro-N-phenylpropanamide. Amber glass. MS (ES) m/e 475.4 $[M+H]^+$.

Example 5: Preparation of N-[3-(piperidin-1-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 1 substituting piperidine for 2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride and 3-chloro-N-(3, 4-dimethoxyphenyl)propanamide for 3-chloro-N-phenylpropanamide. Amber glass. MS (ES) m/e 473.4 $[M+H]^+$.

Example 6: Preparation of N-[2-(N', N'-dimethylamino)ethyl]-N-phenyl-3, 4-dinitrobenzamide hydrochloride

N, N-Dimethyl-N'-phenylethylenediamine (165 mg, 1.00 mmol) was dissolved in dry methylene chloride, cooled to 0 °C, and treated with 3, 4-dinitrobenzoyl chloride (230 mg, 1.0 mmol). After 10 min the cooling bath was removed and the reaction was stirred for 16h at room temperature. A solid began to form after 1h. The reaction mixture was treated with diethyl ether (2 mL) and the pale yellow solid was filtered off, washed with diethyl ether and dried. Obtained the title compound (363 mg, 92%) as a hydrochloride salt. MS (ES) m/e 359.3 $[M+H]^+$, free base; 314.3 $[M-NMe_2]^+$.

Example 7: Preparation of N-(3-methylbutyl)-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide

3, 4-Dimethoxyaniline (1.0 g, 6.5 mmol) was dissolved in methylene chloride and treated with triethylamine (1.5 mL, 10.7 mmol), 4-(N, N-dimethylamino)pyridine (80 mg, 0.65 mmol), and cooled in an ice water bath. The reaction solution was treated dropwise with isovaleryl chloride (0.88 mL, 7.2 mmol). After the addition the cooling bath was removed and the reaction was allowed to stir at room temperature for 16h. The reaction was diluted with ethyl acetate and washed with water, 5% HCl, 5% Na_2CO_3, and brine. The organic

layer was dried over Na_2SO_4, filtered, and evaporated to give a pinkish amorphous solid.

The amide obtained above (475 mg, 2.0 mmol) was dissolved in dry tetrahydrofuran (10 mL) and treated with lithium aluminum hydride (115 mg, 3.0 mmol). The reaction was refluxed for 3.5h. The reaction mixture was cooled to 0 °C and quenched with water (1 mL), 10% NaOH (1 mL), and water (1 mL). The solution was then stirred vigorously at room temperature for 15 min. The solution was diluted with ethyl acetate and dried over Na_2SO_4, filtered, and evaporated to give a dark colored oil.

The amine obtained above was dissolved in dry methylene chloride (5 mL), cooled in an ice water bath, and treated sequentially with triethylamine (0.61 mL, 4.37 mmol), 4-(N, N-dimethylamino)pyridine (25 mg, 0.2 mmol), and 3, 4-dinitrobenzoyl chloride (500 mg, 2.17 mmol). The cooling bath was removed and the reaction was stirred at room temperature for 4h. The reaction was diluted with ethyl acetate and washed with 5% HCl, 5% Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The product was purified by flash column chromatography (silica, 25, 30, 35, 40% ethyl acetate in hexane) to give a yellow oil. Crystallization from ethyl acetate and hexane gave the title compound as a yellow crystalline solid. MP 92 -94 °C. Total yield was 626 mg (75% for two steps).

Example 8: Preparation of N-methyl-N-phenyl-3, 4-dinitrobenzamide

N-Methylaniline (96.3 mg, 0.9 mmol) in dry methylene chloride (6 mL) was treated with triethylamine (101 mg, 140 uL, 1.0 mmol) followed by a solution of 3, 4-dinitrobenzoyl chloride (230 mg, 1.0 mmol) in methylene chloride (1.0 mL). The reaction solution was placed on a shaker overnight at room temperature. The solution was stripped to dryness; the solid was triturated with ether (15 mL) and collected by filtration; the solids were rinsed with water and dried *in vacuo* to give the title compound as dusty shrimp colored crystals (128 mg, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s,1H), 7.65 (dd, 2H), 7.26-7.36(m, 3H), 7.07 (d, 2H), 3.54 (s, 3H).

Example 9: Preparation of N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 3, 4-dimethoxyaniline for N-methylaniline. Orange amorphous solid. MS (ES) m/e 346.3 $[M-H]^-$.

Example 10: Preparation of N-benzyl-N-phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting N-benzylaniline for N-methylaniline. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.61-7.70 (m, 2H), 7.24-7.30 (m, 8H), 6.92 (s, 2H), 5.12 (s, 2H).

Example 11: Preparation of N-isopropyl-N-phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting N-isopropylaniline for N-methylaniline. ^{1}H NMR (250 MHz, $CDCl_3$+MeOH-d_4) δ 7.72 (s, 1H), 7.58 (dd, 2H), 7.25-7.27 (m, 3H), 6.98-7.00 (m, 2H), 4.93-5.03 (m, 1H), 3.05-3.60 (m, 6H).

Example 12: Preparation of N-(4-pyridyl)-N-phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 4-aminopyridine for N-methylaniline. ^{1}H NMR (400 MHz, $CDCl_3$+ MeOH-d_4) δ 8.46 (d, 1H), 8.29-8.31 (m, 2H), 8.22-8.24 (dd, 1H), 7.92 (d, 1H), 7.61 (dd, 2H).

Example 13: Preparation of N-(4-nitrophenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 4-nitroaniline for N-methylaniline. ^{1}H NMR (400 MHz, $CDCl_3$+ MeOH-d_4) δ 8.44 (d, 1H), 8.20-8.23 (m, 1H), 8.04-8.07 (m, 2H), 7.90 (d, 1H), 7.76-7.79 (m, 2H).

Example 14: Preparation of N-(3-fluoro-2-methyl)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 3-fluoro-2-methylaniline for N-methylaniline. MS (ES) m/e 318.3 $[M-H]^-$.

Example 15: Preparation of N-(3, 4-dichloro)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 3, 4-dichloroaniline for N-methylaniline. MS (ES) m/e 354.2, 356.2 $[M-H]^-$.

Example 16: Preparation of N-(4-phenoxy)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 4-phenoxyaniline for N-methylaniline. MS (ES) m/e 378.3 $[M-H]^-$.

Example 17: Preparation of N-(2, 4, 6-trichloro)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2, 4, 6-trichloroaniline for N-methylaniline. ^1H NMR (250 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.25-8.50 (m, 3H), 7.99 (s, 1H).

Example 18: Preparation of N-(4-bromo-2-methyl)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 4-bromo-2-methylaniline for N-methylaniline. MS (ES) m/e 378.1 $[M-H]^-$.

Example 19: Preparation of N-(2, 2-diphenyl)ethyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2, 2-diphenylethylamine for N-methylaniline. MS (ES) m/e 390.4 $[M-H]^-$.

Example 20: Preparation of N-(3-methylisoxazol-5-yl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 5-amino-3-methylisoxazole for N-methylaniline. MS (ES) m/e 291.2 $[M-H]^-$.

Example 21: Preparation of N-(2, 6-diethyl)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2, 6-diethylaniline for N-methylaniline. ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H), 8.23-8.25 (m, 1H), 7.98 (d, 1H), 7.69 (s,1H), 7.30-7.34 (m, 1H), 7.19 (d, 1H), 2.60 (q, 4H), 1.20 (t, 6H).

Example 22. Preparation of N-(5, 6, 7, 8-tetrahydronaphth-1-yl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 1-amino-5, 6, 7, 8-tetrahydronaphthalene for N-methylaniline. ^1H NMR (250 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.37-8.50 (m, 2H), 7.01-7.65 (m, 3H) 3.33 (s, 2H), 2.55-2.85 (m, 6H).

Example 23: Preparation of N-(4-chloro-2-nitro)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 4-chloro-2-nitroaniline for N-methylaniline. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.72 (d, 1H), 8.42-8.46 (m, 2H), 8.17 (d, 1H), 7.91 (dd, 1H), 7.71 (d, 1H).

Example 24: Preparation of N-(1-indolinyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting indoline for N-methylaniline. ^{1}H NMR (400 MHz, $CDCl_3$+MeOH-d_4) δ 8.06 (s, 1H), 7.86-7.98 (dd, 2H), 7.17-7.19 (d, 1H), 6.80-7.16 (m, 2H), 3.85-4.30 (m, 2H), 3.10 (t, 2H).

Example 25: Preparation of N-(6-methyl-1, 2, 3, 4-tetrahydroquinolin-1-yl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 6-methyl-1, 2, 3, 4-tetrahydroquinoline for N-methylaniline. ^{1}H NMR (400 MHz, $CDCl_3$+MeOH-d_4) δ 7.93 (s, 1H), 7.49-7.72 (dd, 2H), 7.27 (s, 1H), 6.93 (s, 1H), 6.63 (d, 1H), 3.78-3.83 (m, 2H), 2.69-2.73 (m, 2H), 2.16 (s, 1H), 1.95-1.98 (m, 2H).

Example 26: Preparation of N-[2-(4-methylpiperazin-1-yl)]ethyl-N-phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 1 using chloroacetyl chloride, and N-methylpiperazine. MS (ES) m/e 414.5 $[M+H]^+$.

Example 27: Preparation of N-[2-(morpholin-4-yl)]ethyl-N-(2-methylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 1 using chloroacetyl chloride ortho toluidine, and morpholine. MS (ES) m/e 415.4 $[M+H]^+$.

Example 28: N, N-Diphenyl-3, 4-dinitrobenzamide

A solution of diphenylamine (0.1 g, 0.59 mmol) in dry tetrahydrofuran (1.5 mL) was cooled to 0 °C and treated with sodium hydride (35 mg, 0.89 mmol). The

resulting mixture was stirred at room temperature for 5 minutes, cooled to 0 °C, and treated with 3, 4-dinitrobenzoyl chloride (142 mg, 0.62 mmol). The resulting dirty red solution was gradually warmed to room temperature and stirred for 20 h. TLC revealed the presence of a small amount of the unreacted diphenylamine. A catalytic amount of 4-dimethylaminopyridine (7.2 mg, 0.06 mmol) was added to the reaction mixture and the reaction was stirred for an additional 3 h. The reaction was diluted with methylene chloride and washed with 10% HCl, H_2O, saturated $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a reddish brown oil. Trituration of the crude oil with methanol afforded the title compound as a tan solid (66 mg, 31%). MS (ES) m/e 364.1 $[M+H]^+$.

The following compounds were prepared according to Example 8 using the appropriate amines and 3, 4-dinitrobenzoyl chloride unless otherwise noted.

Example 29: N-(2-Methylphenyl)-3, 4-dinitrobenzamide

^1H NMR(400 MHz, $CDCl_3$+MeOH-d_4) δ 8.50 (d, 1H), 8.25 (dd, 1H), 7.95 (d,.1H), 7.10 (m, 4H), 2.15 (s, 3H).

Example 30: N-Methyl-N-(2-methylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 316.3 $[M+H]^+$, 339.3 $[M+Na]^+$.

Example 31: N-(2-Carboxyphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 330.2 $[M-H]^-$.

Example 32: N-Methyl-N-(2-carboxyphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 344.3 $[M-H]^-$.

Example 33: N-(Phenylmethyl)-3, 4-dinitrobenzamide

MS (ES) m/e 300.2 $[M-H]^-$.

Example 34: N-Methyl-N-(phenylmethyl)-3, 4-dinitrobenzamide

Mp 112-113 °C.

Example 35: N-[2-(Aminocarbonyl)phenyl]-3, 4-dinitrobenzamide

^1H NMR (400 MHz, DMSO-d_6) δ 8.6 (m, 2H), 8.5 (m, 5H), 8.0 (m, 1H), 7.6 (m, 1H), 7.25 (m, 1H).

Example 36: N-[2-(Aminocarbonyl)phenyl]-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 343.3 $[M-H]^-$.

Example 37: N-[2-(Trifluoromethyl)phenyl]-3, 4-dinitrobenzamide

MS (ES) m/e 254.2 $[M-H]^-$.

Example 38: N-Methyl-N-[2-(trifluoromethyl)phenyl]-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.65 (m, 5H), 7.35 (d, 1H), 3.51 (s, 3H).

Example 39: N-(2-Fluorophenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 304.3 $[M-H]^-$.

Example 40: N-(2-Fluorophenyl)-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 320.1 $[M+H]^+$.

Example 41: N-[3-(Aminocarbonyl)phenyl]-3, 4-dinitrobenzamide

MS (ES) m/e 331.2 $[M+H]^+$.

Example 42: N-[3-(Aminocarbonyl)phenyl]-N-methyl-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$+MeOH-d_4) δ 7.72 (s, 1H), 7.55 (m, 3H), 7.4 (m, 1H), 7.15 (t, 1H), 7.0 (d, 1H), 3.3 (s, 3H).

Example 43: N-Pyrazinyl-3, 4-dinitrobenzamide

^1H NMR (400 MHz, DMSO-d_6) δ 9.4 (s, 1H), 8.75 (s, 1H), 8.52 (m, 2H), 8.45 (d, 1H), 8.35 (d, 1H).

Example 44: N-Methyl-N-pyrazinyl-3, 4-dinitrobenzamide

MS (ES) m/e 304.2 $[M+H]^+$.

Example 45: N-(3-Methylpyridin-2-yl)-3, 4-dinitrobenzamide

MS (ES) m/e 303.3 $[M+H]^+$.

Example 46: N-Methyl-N-(3-methylpyridin-2-yl)-3, 4-dinitrobenzamide

MS (ES) m/e 317.2 $[M+H]^+$.

Example 47: N-(2-Cyanophenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 311.3 $[M-H]^-$.

Example 48: N-(2-Cyanophenyl)-N-methyl-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) δ 7.8 (s, 1H), 7.75 (m, 2H), 7.65 (m, 2H), 7.45 (m, 1H), 7.35 (m, 1H), 3.5 (s, 3H).

Example 49: N-(2-Methoxyphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 316.3 $[M-H]^-$.

Example 50: N-(2-Methoxyphenyl)-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 332.2 $[M+H]^+$.

Example 51: N-(2-Biphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 362.3 $[M-H]^-$.

Example 52: N-(2-Biphenyl)-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 378.1 $[M+H]^+$.

Example 53: N-(4-Methoxyphenyl)-N-methyl-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$+MeOH-d_4) δ 7.7 (s, 1H), 7.6 (d, 1H), 7.42 (dd, 1H), 6.8 (d, 2H), 6.65 (d, 2H), 4.15 (s, 3H), 3.55 (s, 3H).

Example 54: N-Methyl-N-[(2-trifluoromethoxy)phenyl]-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.55 (d, 1H), 7.45 (d, 1H), 7.2 (m, 3H), 7.05 (m, 1H), 3.3 (s, 3H).

Example 55: N-(2-Chlorophenyl)-N-methyl-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.72 (m, 2H), 7.48 (m, 1H), 7.35 (m, 3H), 3.46 (s, 3H).

Example 56: N-[2-[(2-Furanylmethyl)aminocarbonyl]phenyl]-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 425.3 $[M+H]^+$.

Example 57: N-Methyl-N-(1-naphthylmethyl)-3, 4-dinitrobenzamide

Mp 119.5-120.5 °C.

Example 58: N-[2-(Methoxycarbonyl)phenyl]-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 360.2 $[M+H]^+$.

Example 59: N-[2-[(2-(3, 4-Dimethoxyphenyl)ethyl)aminocarbonyl]phenyl]-N-methyl-3, 4-dinitrobenzamide

MS (ES) m/e 509.2 $[M+H]^+$.

Example 60: N-Methyl-N-[2-[(2-phenylethyl)aminocarbonyl]phenyl]-3, 4-dinitrobenzamide

MS (ES) m/e 449.3 $[M+H]^+$.

Example 61: N-Pentafluorophenyl-3, 4-dinitrobenzamide

Mp 161-164 °C.

Example 62: N-(2, 6-Dimethylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 316.3 $[M+H]^+$.

Example 63: N-(3-Fluorophenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 304.3 $[M-H]^-$.

Example 64: N-(4-Fluorophenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 304.3 $[M-H]^-$.

Example 65: N-(2-Fluoro-5-methylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 318.3 $[M-H]^-$.

Example 66: N-(4-Methoxy-2-methylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 330.3 $[M-H]^-$.

Example 67: N-(2-Iodophenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 412.2 $[M-H]^-$.

Example 68: N-(2-Chloro-3-methylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 334.2 $[M-H]^-$.

Example 69: N-(2, 4-Dimethylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 314.4 $[M-H]^-$.

Example 70: N-[(2-Chlorophenyl)methyl]-3, 4-dinitrobenzamide

MS (ES) m/e 334.3 $[M-H]^-$.

Example 71: N-[(2-Methylphenyl)methyl]-3, 4-dinitrobenzamide

MS (ES) m/e 314.4 $[M-H]^-$.

Example 72: N-(3-Carboxyphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 330.2 $[M-H]^-$.

Example 73: N-(4-Carboxyphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 330.3 $[M-H]^-$.

Example 74: N-(2, 6-Dichlorophenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 354.3 $[M-H]^-$.

Example 75: N-(1, 3, 4-Thiadiazol-2-yl)-3, 4-dinitrobenzamide

MS (ES) m/e 294.3 $[M-H]^-$.

Example 76: N-(1, 2, 4-Triazol-3-yl)-3, 4-dinitrobenzamide

MS (ES) m/e 296.2 $[M+H]^+$; 294.3 $[M-H]^-$.

Example 77: N-(2-Naphthyl)-3, 4-dinitrobenzamide

^1H NMR(400 MHz, DMSO-d_6) δ 8.75 (d, 1H), 8.51 (dd, 1H), 8.42 (m, 2H), 7.82 (m, 4H), 7.48 (m, 2H).

Example 78: N-(5-Quinolinyl)-3, 4-dinitrobenzamide

Mp 216-218 °C (dec).

Example 79: N-(3-Pyridinyl)-3, 4-dinitrobenzamide

MS (ES) m/e 289.2 $[M+H]^+$.

Example 80: N-(2-Pyridinyl)-3, 4-dinitrobenzamide

MS (ES) m/e 289.2 $[M+H]^+$.

Example 81: N-(6-Fluorobenzothiazol-2-yl)-3, 4-dinitrobenzamide

MS (ES) m/e 363.3 $[M+H]^+$.

Example 82: N-(2-Hydroxyphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 302.3 $[M-H]^-$.

Example 83: N-(1-Naphthyl)-3, 4-dinitrobenzamide

MS (ES) m/e 336.3 $[M-H]^-$.

Example 84: N-(Diphenylmethyl)-3, 4-dinitrobenzamide

MS (ES) m/e 376.2 $[M-H]^-$.

Example 85: N-[4-(N', N'-Dimethylamino)phenyl]-3, 4-dinitrobenzamide

MS (ES) m/e 331.2 $[M+H]^+$.

Example 86: N-[2-(N', N'-Dimethylamino)phenyl]-3, 4-dinitrobenzamide

MS (ES) m/e 331.2 $[M+H]^+$.

Example 87: N-(2-Ethylphenyl)-3, 4-dinitrobenzamide

MS (ES) m/e 314.2 $[M-H]^-$.

Example 88: N-(1-Indazolyl)-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) d 8.75 (s, 1H), 8.56 (m, 2H), 8.27 (s, 1H), 8.04 (d, 1H), 7.84 (d, 1H), 7.67 (t, 1H), 7.49 (t, 1H).

Example 89: N-(1-Benzimidazolyl)-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) d 8.47 (s, 1H), 8.24 (m, 4H), 7.86 (dd, 1H), 7.53 (m, 2H).

Example 90: N-[2-(2-Pyridyl)benzimidazol-1-yl]-3, 4-dinitrobenzamide

^1H NMR (400 MHz, $CDCl_3$) d 8.34 (d, 1H), 8.18 (s, 1H), 7.95 (m, 1H), 7.91 (m, 1H), 7.87 (d, 1H), 7.83 (m, 2H), 7.70 (m, 2H), 7.47 (m, 1H).

Example 91: N-[6-Methoxy-2-(methoxycarbonyl)indol-1-yl]-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 28 substituting methyl 6-methoxy-2-indolecarboxylate for diphenylaniline. Orange yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.19 (s, 1H), 7.97-7.98 (m, 2H), 7.61 (d, 1H), 7.53 (s, 1H), 7.44 (s, 1H), 7.03 (dd, 1H), 3.90 (s, 3H), 3.63 (s, 3H).

Example 92: N-(2, 3-Dimethoxyphenyl)-N-methyl-3, 4-dinitrobenzamide

Mp 113-114 °C.

Example 93: N-(2, 3, 4, 5-Tetrahydro-1H-3-benzazepin-3-yl)-3, 4-dinitrobenzamide

MS (ES) m/e 342.4 $[M+H]^+$.

Example 94: Preparation of N-(2, 3, 4, 5-tetrahydro-1H-1-benzazepin-1-yl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2, 3, 4, 5-tetrahydro-1H-1-benzazepine for N-methylaniline. The 2, 3, 4, 5-tetrahydro-1H-1-benzazepine was prepared by the method report by Yamamoto *et al.* in *Tetrahedron Lett.*, **1983**, *24*, 4711-4712. MS (ES) m/e 342.4 $[M+H]^+$.

Example 95: Preparation of N-(2-ethylphenyl)-N-methyl-3, 4-dinitrobenzamide

A solution of the compound of Example 87 (109 mg, 0.35 mmol) in dry tetrahydrofuran (1 mL) under argon was cooled to 0 °C and added (dropwise!) potassium bis(trimethylsilyl)amide (1 mL, 0.53 mmol, 0.5 M solution in toluene). After stirring at 0 °C for 5 minutes, iodomethane was added to the reaction mixture and the reaction was gradually warmed to room temperature and stirred for 20 hours. The reaction was diluted with methylene chloride and washed with H_2O, 5% Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a reddish brown solid. The crude solid was purified by flash column chromatography (silica, 20, 30, and 40% ethyl acetate in hexane) to afford 37 mg (32%) of the title compound as a light yellow solid. MS (ES) m/e 330.2 $[M+H]^+$.

Example 96: Preparation of N-methyl-N-[2-[(4-methylpiperazin-1-yl)carbonyl]phenyl]-3, 4-dinitrobenzamide hydrochloride

The carboxylic acid prepared in Example 32 (2.0 g, 5.8 mmol) in chloroform (25 mL) was treated with thionyl chloride (5 mL) and gently refluxed for 2 h. After cooling to room temperature the solvent and excess reagent were evaporated to give the acid chloride that was used without further purification.

Acid chloride (200 mg, 0.55 mmol) was dissolved in dry methylene chloride (10 mL) and treated with N-methyl piperazine (55.5 uL, 0.5 mmol). The reaction was stirred overnight at RT. The solvent was evaporated and the resulting residue was triturated with diethyl ether to give 99 mg of the desired product. MS (ES) m/e 428.3 $[M+H]^+$.

Example 97: Preparation of N-[[2-[(3-methoxycarbonyl)phenyl]aminocarbonyl]phenyl]-N-methyl-3, 4-dinitrobenzamide

Prepared according to the procedure described for Example 96 substituting methyl 3-aminobenzoate for N-methylpiperazine. MS (ES) m/e 477.2 $[M-H]^-$.

Example 98: Preparation of N-methyl-N-[[2-[2-(N', N'-dimethylamino)phenyl]aminocarbonyl]phenyl]-3, 4-dinitrobenzamide

Prepared according to the procedure described for Example 96 substituting 2-(N, N-dimethylamino)aniline for N-methylpiperazine. MS (ES) m/e 464.3 $[M+H]^+$.

Example 99: Preparation of (*S*)-N-methyl-N-[[2-[1-(tert-butoxycarbonyl)-2-phenylethyl]aminocarbonyl]phenyl]-3, 4-dinitrobenzamide

Prepared according to the procedure described for Example 96 substituting L-phenylalanine tert-butyl ester for N-methylpiperazine. MS (ES) m/e 547.1 $[MH]^-$

Example 100: Preparation of N-[[2-[2-(ethoxycarbonyl)ethyl]aminocarbonyl]phenyl]-N-methyl-3, 4-dinitrobenzamide

Prepared according to the procedure described for Example 96 substituting beta alanine ethyl ester for N-methylpiperazine. MS (ES) m/e 445.1 $[M+H]^+$.

Example 101: Preparation of (*S*)-N-[[2-[1-(aminocarbonyl)-2-phenylethyl]aminocarbonyl]phenyl]-N-methyl-3, 4-dinitrobenzamide

Prepared according to the procedure described for Example 96 substituting L-phenylalaninamide for N-methylpiperazine. MS (ES) m/e 492.1 $[M+H]^+$.

Example 102: Preparation of (S)-N-[[2-[1-carboxy-2-phenylethyl]aminocarbonyl]phenyl]-N-methyl-3, 4-dinitrobenzamide

Tert-butyl ester prepared in Example 99 (50 mg, 0.091 mmol) was treated with cold (0 °C) TFA (3 mL) and stirred at 0 °C for 0.5 h and then at RT for 2 h. Evaporation and trituration of the resulting residue with water gave 29 mg of the desired compound. Mp 96-106 °C.

Example 103: Preparation of N-(2-ethylphenyl)-N-[2-(tert-butoxycarbonyl)ethyl]-3, 4-dinitrobenzamide

a) Tert-butyl 3-(N-2-ethylphenyl)amino proprionate

A solution of 2-ethylaniline (12.1g, 100 mmol), tert-butyl acrylate (12.8 g, 100 mmol), and glacial acetic acid (2.5 mL) was gently refluxed for 24 h. The solvents were evaporated under reduced pressure; the viscous residue was taken up in diethyl ether (200 mL) and the resulting solution was washed in turn with dilute aqueous sodium bicarbonate solution and water and dried (Na_2SO_4). Evaporation of the solvent gave a viscous syrup which was purified by flash column chromatography (silica, 10, 15% ethyl acetate in hexane) to give 4.15 g (17%) of a viscous yellow oil. MS(ES) m/e 250.3 $[M+H]^+$.

b) N-(2-Ethylphenyl)-N-[2-(tert-butyloxycarbonyl)ethyl]-3, 4-dinitrobenzamide

A solution of tert-butyl ester from Example 103a (498 mg, 2.0 mmol), 3, 4-dinitrobenzoyl chloride (483 mg, 2.0 mmol), and triethylamine (280 uL, 2.0 mmol) in methylene chloride (10 mL) was stirred overnight at room temperature. The reaction mixture was washed in turn with water, dilute aqueous sodium bicarbonate solution, dilute aqueous hydrochloric acid, and water and dried (Na_2SO_4). Evaporation provided 890 mg (100%) of the desired product as a viscous amber syrup. MS(ES) m/e 466.2 $[M+Na]^+$.

Example 104: Preparation of N-(2-carboxyethyl)-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

N-(2-Ethylphenyl)-N-[2-(tert-butyloxycarbonyl)ethyl]-3, 4-dinitrobenzamide (800mg, 1.80 mmol) from Example 103 was treated at room temperature with a solution of trifluoroacetic acid (20 mL) and methylene chloride (20 mL). The reaction solution was stirred at room temperature for 2 h.

Evaporation provided a syrup that was crystallized from diethyl ether and hexane to give 550 mg (79%) of the desired product. MS (ES) m/e 386.2 $[M-H]^-$.

Example 105: Preparation of N-[2-(ethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

A solution of the compound of Example 104 (150 mg, 0.387 mmol) in dry methylene chloride (15 mL) was cooled to 0 °C and treated with oxalyl chloride (3.87 mL) and a catalytic amount of N, N-dimethylformamide (5 uL). The resulting mixture was gradually warmed to room temperature and stirred for 20 hours. The methylene chloride and excess oxalyl chloride were removed at reduced pressure, and the resulting golden yellow oil (acid chloride) was pump-dried for 30 minutes and used directly in the following step.

A solution of the crude acid chloride (0.129 mmol) in methylene chloride (5 mL) was introduced into a cooled (0 °C) reaction mixture of ethylamine (77 uL, 0.155 mmol, 2M solution in tetrahydrofuran), triethylamine (27 uL, 0.19 mmol) and 4-dimethylaminopyridine (1 mg, 0.0065 mmol). After stirring for 1 hour, the reaction was diluted with methylene chloride and washed with 10% HCl, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude oil. The crude product was purified by flash column chromatography (silica, 1 and 5% methanol in methylene chloride) to afford 46 mg (86%) of the title compound as a viscous golden yellow oil. MS (ES) m/e 415.3 $[M+H]^+$.

Example 106: Preparation of N-[2-(diethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 105 substituting diethylamine for ethylamine. Light yellow solid. MS (ES) m/e 443.2 $[M+H]^+$.

Example 107: Preparation of N-(2, 6-diisopropyl)phenyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2, 6-diisopropylaniline for N-methylaniline. White, amorphous solid. MS (ES) m/e 370.3 $[M-H]^-$.

Example 108: Preparation of N-[2-(aminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 105 substituting ammonium hydroxide for ethylamine. Bright yellow solid. MS (ES) m/e 387.2 $[M+H]^+$.

Example 109: Preparation of N-(2, 6-diethyl)phenyl-N-methyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 95 substituting the compound of Example 21 for the compound of Example 87. Yellow solid. ^1H NMR (400 MHz, $CDCl_3$) d 7.75 (s, 1H), 7.60-7.67 (m, 2H), 7.26-7.30 (m, 1H), 7.13 (d, 2H), 3.38 (t, 3H), 2.58-2.66 (m, 2H), 2.42-2.52 (m, 2H), 1.24 (t, 6H).

Example 110: Preparation of N-[2-[(1-piperidinyl)carbonyl]ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 105 substituting piperidine for ethylamine. Pale yellow solid. MS (ES) m/e 455.3 $[M+H]^+$.

Example 111: Preparation of N-[2-[(N'-benzyl-N'-methylamino)carbonyl]ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 105 substituting N-benzyl-N-methylamine for ethylamine. Golden yellow oil. MS (ES) m/e 491.2 $[M+H]^+$.

Example 112: Preparation of N-(2, 6-diisopropyl)phenyl-N-methyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 95 substituting the compound of Example 107 for the compound of Example 87. Light yellow solid. MS (ES) m/e 386.4 $[M+H]^+$.

Example 113: Preparation of N-(2-n-butylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2-n-butylaniline for N-methylaniline. Off-white solid. MS (ES) m/e 342.3 $[M-H]^-$.

Example 114: Preparation of N-(2-isopropylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 8 substituting 2-isopropylaniline for N-methylaniline. Off-white solid. MS (ES) m/e 328.1 $[M-H]^-$.

Example 115: Preparation of N-(2-butylphenyl)-N-methyl-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 95 substituting the compound of Example 113 for the compound of Example 87. Golden brown oil. ^1H NMR (400 MHz, $CDCl_3$) d 7.80 (s, 1H), 7.61-7.68 (m, 2H), 7.16-7.29 (m, 3H), 7.08 (d, 1H), 3.44 (t, 3H), 2.49-2.60 (m, 1H), 2.35-2.45 (m, 1H), 1.48-1.67 (m, 2H), 1.36-1.45 (m, 2H), 0.95 (t, 3H).

Example 116: Preparation of N-[2-(morpholinocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 105 substituting morpholine for ethylamine. Pale amber glass. MS (ES) m/e 457.3 $[M+H]^+$.

Example 117. Preparation of N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

a) N-[3-[(Diethylamino)carbonyl]propyl]-2-ethylaniline

A solution of diethylamine (1.4 mL, 13.7 mmol) in methylene chloride (20mL) was cooled to 0 °C and treated with triethylamine (2.1 mL, 15 mmol) and 4-chlorobutyryl chloride (1.7 mL, 15 mmol). The resulting mixture was gradually warmed to room temperature and stirred for 20 h. The reaction was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was pump-dried overnight and used directly in the following step.

A solution of 2-ethylaniline (250 mg, 2.06 mmol) in N, N-dimethylformamide (6 mL) was treated with the crude chloride prepared above (550 mg, 3.1 mmol), triethylamine (0.48 mL, 3.4 mmol), and tetra-*n*-butylammonium iodide (74 mg, 0.2 mmol). The resulting mixture was stirred at 90 °C for 20 hours. The reaction was diluted with ethyl acetate and washed with water, 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 20:10:70 and 30:10:60 ethyl acetate-methylene chloride-hexane) to afford the title compound (215 mg, 40%) as a viscous light

brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.11 (t, 1H), 7.06 (d, 1H), 6.69 (t, 1H), 6.61 (d, 1H), 4.10 (bs, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 3.21 (t, 2H), 2.62-2.40 (m, 4H), 2.13-2.02 (m, 2H), 1.25 (t, 3H), 1.08-1.24 (m, 6H).

b) N-[3-[(Diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

A solution of the compound of Example 117(a) (211 mg, 0.807 mmol) in methylene chloride (2.2 mL) was cooled to 0 °C and treated with triethylamine (0.12 mL, 0.85 mmol) and 3, 4-dinitrobenzoyl chloride (195 mg, 0.85 mmol). The resulting mixture was gradually warmed to room temperature and stirred for 20 h. The reaction was diluted with methylene chloride and washed with 10% HCl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography (silica, 30:10:60, 40:10:50, and 50:10:40 ethyl acetate-methylene chloride-hexane) to afford the title compound (242 mg, 66%) as a golden yellow oil. MS (ES) m/e 457.1 $[M+H]^+$.

Example 118. Preparation of N-(3-oxo-3-phenylpropyl)-N-(2-ethylphenyl)-3, 4-dinitrobenzamide

This compound was prepared according to the procedure described for Example 117 substituting 3-chloropropiophenone as the alkylating agent. MS (ES) m/e 917.1 $[2M+Na]^+$, 1364 $[3M+Na]^+$.

BIOLOGICAL DATA

Effect of Compounds on the CGRP Receptor

The test compounds were assayed for the inhibition of [^{125}I] CGRP (obtained from Amersham, Chicago, IL) binding and CGRP-activated adenylate cyclase activity.

SK-N-MC cells were obtained from American Type Culture Collection (Rockville, MD) and grown in Minimum Essential Media ("MEM") medium containing fetal calf serum (10%). Cells were grown in T-150 flasks or Costar multiwell plates (24 well) and maintained at 37 °C in a 90% humidified incubator with an atmosphere of 5% CO_2 and 95% air.

[^{125}I] CGRP Binding assay:

SK-N-MC cells were homogenized in 5 mM Tris-HCl pH 7.4, 10 mM Na-EDTA and the homogenate was centrifuged at 48,000 g for 20 min at 4 °C. The pellet was resuspended in 20 mM Na-HEPES pH 7.4, 10 mM $MgCl_2$ and

recentrifuged as above. The membrane pellets were resuspended in the same buffer and stored frozen at -70 °C. The protein concentration was measured by the Pierce BCA method using bovine serum albumin as the standard.

The [^{125}I] CGRP receptor binding assay was performed using a buffer containing 20 mM Na-HEPES pH 7.4, 10 mM $MgCl_2$, 0.05% BSA and 0.1 mg/mL bacitracin. The membranes (50 ug protein/mL) were incubated with various concentrations (1, 10, 30, 60 and 100 uM) of the test compounds and 40 pM [^{125}I] CGRP in a total volume of 500 uL. for 60 min at 25 °C. The reaction was terminated by addition of 2 mL ice-cold 0.9% NaCl, followed by rapid filtration through Skatron Filtermates presoaked in 0.5% polyethylenimine PEI). The filters were rinsed twice with 2 mL of cold 0.9% NaCl and the radioactivity counted in a gamma counter. All binding data was analyzed by computer assisted LIGAND 2 program.

Adenylate cyclase activity:

Adenylate cyclase activity was measured in triplicate as the rate of conversion of α[^{32}P]ATP to [^{32}P]cAMP as previously described (Aiyer et al., *Endocrinology*, Vol. 129, pp 965-969 (1991)). Human neuroblastoma cell (SK-N-MC) membranes [40-60 µg] were incubated in triplicate in buffer containing 50 mM Tris-HCl (pH 7.4), 10 nM $MgCl_2$, 1.2 mM ATP, 1.0 µCi α[^{32}P]ATP, 0.1 mM cAMP, 2.8 nM phosphoenolpyruvate and 5.2 µg/ml myokinase in a final volume of 100 µl for 20 min at 30°C. The reactions were stopped with 1 ml solution containing cAMP, ATP and 22000 cpm of [^{3}H] cAMP. [^{32}P]cAMP was separated using sequential chromatography (Dowex and alumina columns) (Salmon et al., *Ana..Biochem.* Vol. 58, pp. 541-548 (1974)). Adenylate cyclase activities were determined in the absence (basal) or presence of 2.5 nM of hCGRPα with various concentrations (0.1 µM to 30 µM) of compound.

The compounds of this invention show CGRP receptor antagonist activity having IC_{50} values in the range of 0.001 to 100 µM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are ligands of the CGRP receptor and which bind thereto with an IC_{50} value in the range of 0.001 to 100 µM.

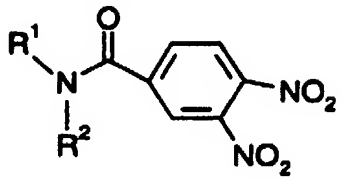
All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if

each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

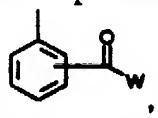
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

R^1 is hydrogen, methyl, -$(CH_2)_n$, branched (3-6 carbon) alkyl, -$(CH_2)_n$phenyl, -$(CH_2)_n$-N(-$(CH_2)_m$-X-$(CH_2)_m$-), wherein X is CH_2, oxygen or N-alkyl, or R^1 is $(CH_2)_nNR^3R^4$, or $(CH_2)_nZ$, wherein Z is CO_2H, CO_2-alkyl, $CONR^3R^4$, $-N(R^3)CO_2R^3$, $-N(R^3)C(O)NR^3R^4$, $-OC(O)NR^3R^4$, or COR^5, and wherein R^3 and R^4 are independently hydrogen, C_{1-4}alkyl or C_{1-4}alkylphenyl, or together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring, wherein the heteroring is optionally fused to an optionally substituted phenyl ring, and R^5 is methyl, trifluoromethyl, C_{2-6}alkyl, phenyl or heteroaryl;

R^2 is optionally substituted aryl or heteroaryl, or R^2 is A-Ar, wherein A is lower alkyl (C_{1-4}) or branched alkyl, wherein a branch may contain a substituted phenyl ring, and Ar is substituted phenyl or a substituted 5- or 6-membered heteroaryl ring which optionally contains one or more heteroatoms selected from N, O or S, or R^2 is  , wherein W is OH, NR^3R^4, O-alkyl, an amide derived from an amino acid, NR^6R^7, where R^6 is H, alkyl, and R^7 is aryl or substituted aryl, $(CH_2)_n$-aryl, $(CH_2)_n$-substituted aryl, $(CH_2)_n$-heteroaryl, or $(CH_2)_n$-Z; or

R^1 and R^2 together with the nitrogen to which they are attached form a 5- or 6-membered heteroring fused to an optionally substituted phenyl ring;

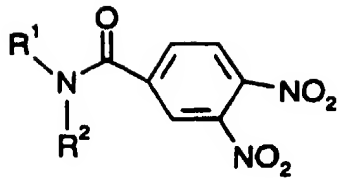
m is 1 to 3; and

n is 1 to 6, provided that the compound is not N-3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1-H-3-benzazepine-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3,4-dinitrobenzamide or N-phenyl-3,4-dinitrobenzamide.

2. The compound as claimed in claim 1 selected from:
N-(2-ethylphenyl)-N-[2-(tert-butoxycarbonyl)ethyl]-3, 4-dinitrobenzamide;
N-[2-(morpholinocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-(ethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-(diethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-[(1-piperidinyl)carbonyl]ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-(3-oxo-3-phenylpropyl)-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-Methyl-N-(2-methylphenyl)-3, 4-dinitrobenzamide;
N-(2-ethylphenyl)-N-methyl-3, 4-dinitrobenzamide;
N-(2, 6-diethyl)phenyl-N-methyl-3, 4-dinitrobenzamide;
N-[3-(2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(7, 8-dimethoxy-2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(N'-methyl-2-phenylethylamino)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(morpholin-4-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide;
N-[3-(piperidin-1-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide;
N-[2-(N', N'-dimethylamino)ethyl]-N-phenyl-3, 4-dinitrobenzamide;
N-(3-methylbutyl)-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide; and
N-methyl-N-phenyl-3, 4-dinitrobenzamide.

3. A pharmaceutical composition comprising a compound of formula (I) according to claim 1 and a pharmaceutically acceptable carrier.

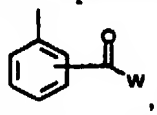
4. A method of treating a CGRP-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

R^1 is hydrogen, methyl, -$(CH_2)_n$, branched (3-6 carbon) alkyl, -$(CH_2)_n$phenyl, -$(CH_2)_n$-N(-$(CH_2)_m$-X-$(CH_2)_m$-), wherein X is CH_2, oxygen or N-alkyl, or R^1 is $(CH_2)_nNR^3R^4$, or $(CH_2)_nZ$, wherein Z is CO_2H, CO_2-alkyl, $CONR^3R^4$, $-N(R^3)CO_2R^3$, $-N(R^3)C(O)NR^3R^4$, $-OC(O)NR^3R^4$,or COR^5, and wherein R^3 and R^4 are independently hydrogen, C_{1-4}alkyl or C_{1-4}alkylphenyl, or together with the nitrogen to which they are attached, form a 5-, 6-, or 7-membered heteroring, wherein the heteroring is optionally fused to an optionally substituted phenyl ring, and R^5 is methyl, trifluoromethyl, C_{2-6}alkyl, phenyl or heteroaryl;

R^2 is optionally substituted aryl or heteroaryl, or R^2 is A-Ar, wherein A is lower alkyl (C_{1-4}) or branched alkyl, wherein a branch may contain a substituted phenyl ring, and Ar is substituted phenyl or a substituted 5- or 6-membered heteroaryl ring which optionally contains one or more heteroatoms selected from N, O or S, or R^2 is  , wherein W is OH, NR^3R^4, O-alkyl, an amide derived from an amino acid, NR^6R^7, where R^6 is H, alkyl, and R^7 is aryl or substituted aryl, $(CH_2)_n$-aryl, $(CH_2)_n$-substituted aryl, $(CH_2)_n$-heteroaryl, or $(CH_2)_n$-Z; or

R^1 and R^2 together with the nitrogen to which they are attached form a 5- or 6-membered heteroring fused to an optionally substituted phenyl ring;

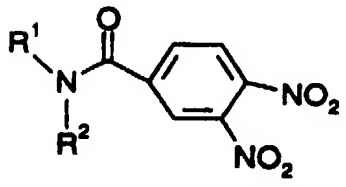
m is 1 to 3; and

n is 1 to 6, provided that the compound is not N-3-(2,3,4,5-tetrahydro-7,8-dimethoxy-1-H-3-benzazepine-3-yl)propyl]-N-(3,4-dimethoxyphenyl)-3,4-dinitrobenzamide or N-phenyl-3,4-dinitrobenzamide.

5. The method as claimed in claim 4 wherein the compound of formula (I) is a compound selected from:

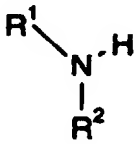
N-(2-ethylphenyl)-N-[2-(tert-butoxycarbonyl)ethyl]-3, 4-dinitrobenzamide;
N-[2-(morpholinocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-(ethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-(diethylaminocarbonyl)ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[2-[(1-piperidinyl)carbonyl]ethyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-[3-[(diethylamino)carbonyl]propyl]-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-(3-oxo-3-phenylpropyl)-N-(2-ethylphenyl)-3, 4-dinitrobenzamide;
N-Methyl-N-(2-methylphenyl)-3, 4-dinitrobenzamide;
N-(2-ethylphenyl)-N-methyl-3, 4-dinitrobenzamide;
N-(2, 6-diethyl)phenyl-N-methyl-3, 4-dinitrobenzamide;
N-[3-(2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(7, 8-dimethoxy-2, 3, 4, 5-terahydro-1H-3-benzazepin-3-yl)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(N'-methyl-2-phenylethylamino)propyl]-N-phenyl-3, 4-dinitrobenzamide;
N-[3-(morpholin-4-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide;
N-[3-(piperidin-1-yl)propyl]-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide;
N-[2-(N', N'-dimethylamino)ethyl]-N-phenyl-3, 4-dinitrobenzamide;
N-(3-methylbutyl)-N-(3, 4-dimethoxyphenyl)-3, 4-dinitrobenzamide; and
N-methyl-N-phenyl-3, 4-dinitrobenzamide.

6. A process for preparing a compound defined in claim 1 having the structure of formula (I)



Formula (I)

which comprises reacting a suitable acid chloride compound derived from 3, 4-dinitrobenzoic acid, with a compound of formula (II)



Formula (II)

wherein R^1 and R^2 are defined in claim 1, in the presence of an amine base.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15931

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55; C07D 223/16
US CL :514/213; 540/594

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/213; 540/594

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAPLUS on STN, Chemical Abstracts Service, (Columbus, Ohio), Accession No. 1995:42025, Nadler et al, WO 942791, Published 08 December 1996, Abstract.	1-6, in part

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 OCTOBER 1997	Date of mailing of the international search report 17 NOV 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer R. W. RAMSUER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15931

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6, in part,
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15931

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. R1,R2,R3,R4,R5,X,Z,m,n, the proviso,etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a dinitrophenylcarbonylamino group which does not define a contribution over the prior art. Therefore, the first discernible invention as found in Example 1,(the compound therein, the pharmaceutical composition therewith, the method of preparation thereof and the method of treating migraines therewith) has been searched.